Constitutional Hypothesis. The document has answered (170) Seltzer by stating that his views are contrary to those of most researchers in this field. The article is reproduced in its entirety.

The Effect of Cigarette Smoking on Coronary Heart Disease

Where Do We Stand Now?

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IT IS AN ESTABLISHED observation that there is a statistically significant association of cigarette smokers and increased mortality and morbidity from coronary heart disease (CHD) in men. It forms the basic springboard for public health warnings as to the health hazards of cigarette smoking and CHD. But it does not tell us how smoking causes or precipitates a death from CHD, or if indeed it does. The most such an observation can do is to demonstrate the existence of a relationship; it cannot establish any existing relationship as a causal one. For this, it is necessary to derive biological inferences from other evidence, pathological, clinical, experimental, as well as epidemiological. What follows is an analysis as to where we are now with respect to the biological inferences, and not necessarily where we will be in the future, since all the facts are not yet in and many of the conclusions and concepts will need more documentation.

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A convenient starting point is the *Surgeon General's Advisory Committee's Report* of 1964. After considering all the available information on smoking and CHD, the committee concluded that "male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance."[1] However, since 1964 there has accumulated a considerable body of data bearing on this area of concern, and it is from this additional evidence that we can best judge where we now stand on the effect of smoking on CHD. Epidemiological, pathological, experimental, and clinical evidence will be examined in turn.

Epidemiological Evidence

Recently, I reviewed the new epidemiological evidence.[2] The conclusion of the Surgeon General's 1964 report that male cigarette smokers have a higher death rate from CHD than men who do not smoke has been confirmed in the new studies published since the report was issued. Prospective studies of smoking and death rate gave a median mortality ratio (current cigarette smokers to nonsmokers) of 1.7, with no appreciable excess in deaths among cigar and pipe smokers. Angina pectoris, which represents about 20% of all manifestations of CHD, was fo

the most part found to be unrelated to cigarette smoking. Significantly, duration of cigarette smoking was found to be unassociated with excess CHD mortality, and conflicting results were obtained with regard to the effect of cigarette smoke inhalation. There also were a number of inconsistencies and inversions in reports of a consistent, rising gradient of CHD mortality with increasing amounts of cigarettes smoked. Those who smoked the most cigarettes had higher CHD rates than those who smoked the least, but the disease rates of the those smoking intermediate amounts were almost invariably the same or lower than those of those who smoked the least. The data dealing with discontinuance of smoking gave contractory and inconsistent findings and reflected on the problem of drawing valid conclusions from such data in exsmokers. In sum, collateral epidemiological evidence related to reasonable mechanisms was found to be weak, negative, or nonsupportive.

This in no way obviates the basic observation that cigarette smokers show excess mortality and disability from CHD, including sudden death. This observation still stands and commands attention and explanation. It means that the collateral epidemiological evidence is not supportive with respect to CHD as similar evidence is for smoking and other diseases, such as lung cancer and chronic bronchitis.

Pathological Evidence

It has been hypothesized that cigarette smoking has a long-term effect on CHD through a cumulative process of augmentation of atherogenesis.[3] The studies of Auerback et al[5] and Strong et al[6] in hospital autopsy cases found advanced degrees of atherosclerosis to be higher among cigarette smokers than among nonsmokers and increased with amount of smoking.

In more recent studies of populations likely to be less selected for arterial disease or smoking habit, Viel and associates[8] found "no relationship between atherosclerotic lesions and the use of tobacco" in an autopsy study of violent deaths (ages 10 to 70 years). In another study of violent deaths among consecutive accident victims (ages 16 to 49 years) Benson and Galindo (written communication, Jan 1968) found no significant differences in amount and type of atherosclerosis between smokers and nonsmokers. As noted by W. Kannel, MD (oral communication, August 1969), the autopsy series of the Framingham Study shows no correlation of degree of uncomplicated coronary artery atherosclerosis and the antecedent premorbid cigarette smoking habit.

That cigarette smoking has a chronic or cumulative effect leading to advanced degrees of atherogenesis is, also, inconsistent with several established observations: that duration of cigarette smoking is not associated with excess deaths from CHD,[7-9] with the lack of uniform evidence of an association of cigarette smoking with angina pectoris, and with the decreased statistical association of cigarette smoking and CHD in older subjects. The evidence, then, for a long-term effect of cigarette smoking contributing to excess CHD through a process of augmentation of atherosclerosis is not clear-cut, and is inconsistent with other pertinent information.

Clinical and Experimental Evidence

This section deals with the acute effects of cigarette smoking. These effects rather than the possible long-term effects of smoking are the present major basis of suspicion of harm to the cardiovascular system.[10] Of the various components of tobacco smoke with acute pharmacologic effects, the focus until recently was almost exclusively on nicotine. Lately, other constituents of tobacco smoke, principally carbon monoxide, have also been receiving attention.

Much is known concerning the acute cardiovascular effects of nicotine in man and experimental animals. In low concentrations, nicotine stimulates the sympathetic and parasympathetic ganglia, and in high concentrations, paralyses them. Thus, nicotine can cause liberation of catecholamines from the adrenal medulla. Nicotine can also have a sympathomimetic effect by causing the discharge of epinephrine and norepinephrine from chromaffin cells in various tissues, and in addition, can produce effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. The net results are transient, noncumulative, reversi-

changes quickly returned to normal, and the fibrillation threshold declined slowly and eventually fell below threshold baseline. As far as studies in humans are concerned, there appear to be no hard facts on this subject, no conclusive evidence that cigarette smoking precipitates "serious, life-threatening arrhythmias." But since arrhythmias can lead to clinical disability and death it is important that this subject be thoroughly investigated.

5. Does cigarette smoking lead to thrombus formation? In the presence of impaired coronary artery circulation, does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through an increase in platelet adhesiveness?

Helpful reviews of the literature on smoking and thrombosis have been provided by Murphy and Mustard[18,19] and again most recently by Murphy.[20] These authors find no satisfactory answer to the question, "Does smoking lead to thrombus formation?" They note that the experimental approach with laboratory animals is replete with difficulties in simulating human cigarette smoking, and that the assessment of thrombosis is a problem since the techniques used do not represent thrombosis but clotting of shed blood. The problem of microthrombi is even more difficult.

Murphy and Mustard note that actual experimental work in connection with smoking and thrombus formation is scanty, and consider inconclusive the results of Engelberg and Futterman,[22] who used the Chandler loop, in which a significant reduction in thrombus formation time was reported in some subjects after they smoked two cigarettes. In answer to the question, "Which constituents in tobacco smoke are producing the effect?" Murphy and Mustard state that there is "embarrasingly little information" and no formal conclusions can be drawn. They note that the evidence at present is circumstantial while they indicate that "nicotine may be responsible." After consideration of the studies relating the platelet, arterial wall, coagulation, and fibrinolysis to thrombogenesis, the reviewers conclude:

> The evidence, so far, suggests the tentative conclusion that smoking is associated with a transient increase in tendency to form thrombi and this result could be largely explained by the release of endogeneous epinephrine by absorbed nicotine.

Studies of Spain et al[21] and Engelberg and Futterman[22] do ntt support the suggestion that cigarette smoking may precipitate acute coronary artery events by altering the blood coagulability as a result of stimulation to catecholamine production and free fatty acid mobilization.

Because of the difficulty of studying thrombus formation in man, special emphasis has been placed on blood coagulation, even though coagulation and thrombus formation are not identical. In studying possible smoking effects on thrombus formation in man, observers have relied heavily on in vitro phenomena with the attendant problems of experimental control and of transposing in vitro results to intact man. It is possible that clotting may be the least important mechanism in the thrombotic development, and that thrombosis will only occur when vessel damage is present and when there is decreased flow through vasoconstriction.

At the present state of our knowledge, it is possible that release of endogeneous epinephrine through nicotine absorption may produce transient increases in platelet aggregation in some persons. But this evidence is confounded with factors inherent in the nature of the experiments and in man's great variation and unique homeostatic propensities. Even if experimental methods and design were adequate, the question of smoking and thrombus formation would still remain an extremely difficult problem. From the evidence now available, no firm conclusion is possible that cigarette smoking so affects the thrombus forming process in human blood as to account for a portion of the excess deaths from CHD that occur in cigarette smokers.

6. Does the carbon monoxide constituent of cigarette smoke result in or contribute to increased myocardial infarction or sudden death either in normal individuals or in persons with already impaired coronary circulation due to CHD?

Studies have shown that the carbon monoxide constituent of cigarette smoke does effect increases (2% to 10%) in the levels of carboxyhemoglobin (COHb) saturation when heavy cigarette smokers and nonsmok-

ble increases in heart rate; cardiac output, ie, cardiac work; systolic blood pressure; and in rate and depth of breathing.

The Surgeon General's 1964 committee reviewed and analyzed the large body of data available to them on the acute effects of cigarette smoking and found "no unique cardiovascular effects" were demonstrated to "seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease."[1] The conclusions were based on the effects of nicotine; carbon monoxide was not considered.

Since then there has accumulated a considerable amount of additional experimental material. These data have led the Public Health Service to advance the theoretical concept of mechanisms, whereby ". . . in the presence of impaired coronary circulation due to coronary heart disease, cigarette smoking may 'trigger' myocardial oxygen deficits of critical degree" leading to myocardial infarction and sudden death.[10]

Let us examine the more important of these mechanisms. This can be done best by posing a number of questions and attempting to answer them on the basis of the present evidence.

1. Does cigarette smoking "trigger" or "contribute to" increased incidence of acute myocardial infarction or sudden death through critical reductions in coronary nutrient capillary blood flow? The evidence that it could rests on the observations that cigarette smoking creates increased myocardial oxygen demands owing to the nicotine-induced catecholamine effect, and that while in normal persons the response is a compensatory increase in coronary blood flow, in some CHD patients, the compensatory increase in blood flow is absent.[11] The problem then rests on how critical is the absence of compensatory increase in coronary blood flow in persons with already impaired coronary circulation, in the light of differences in amount and frequency of smoking, of the condition and activity level of the patient, and considering that the effects of smoking are transient and noncumulative. The evidence on these points is not yet available; the question is challenging and remains to be answered.

2. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree through "the impairment of coronary blood as a result of the increased blood viscosity associated with hyperlipemia and hemoconcentration"[10] It has been reported that hemoconcentration occurs both in cigarette smokers and in patients with myocardial infarction, and that increased fatty acids increase the force necessary to "shear" blood. However, conflicting results have been obtained with respect to hemoconcentration in persons with CHD.[12,13] The concepts of viscosity of blood as influenced by rate of shear and hematocrit value are presently, as Burch and DePasquale[14] point out, "highly speculative." The whole question is exceedingly complex. There are no data directly relating smoking to fatal CHD events through measurable increased blood viscosity in patients with CHD. This interesting concept is still hypothetical and without documentation.

3. Does cigarette smoking, by a catecholamine effect, "trigger" myocardial oxygen deficit of a critical degree through "the increase of myocardial wall tension and velocity of contraction?"[10] That nicotine or cigarette smoking or both, augment heart muscle contractility and consequently increase myocardial oxygen need, is consistent with the evidence. The extent of the increase in oxygen demand, however, is imperfectly known and dependent on factors involved in the complexity of myocardial energetics and nicotine absorption. Where, when, in what circumstances are the levels of oxygen requirements occasioned by increased myocardial contractility not met? The answer to the question is still to come.

4. Does cigarette smoking "trigger" myocardial oxygen deficit of a critical degree "through a predisposition to acute arrhythmias as a consequence of harmful neurogenic reflexes or catecholamine release?"[10] Support for this hypothesis comes, in part, from experimental studies in dogs in which direct administration of nicotine induced varying effects on the complicated neural and humoral mechanisms affect heart rate and rhythm, and an enhancement of Purkinj fiber "automaticity."[15,16] Webb et al showed, following bipolar ventricular electrode stimulation of dogs, a postresponse to cigarette smoking in which hemodynamic

References

1. "Smoking and Health," in *Report of the Advisory Committee to the Surgeon General*, US Dept of Health, Education and Welfare, Public Health Service, 1964.

2. Seltzer, C.C.: An Evaluation of the Effect of Smoking on Coronary Heart Disease: I. Epidemiological Evidence, *JAMA* 203:193-200 (Jan 15) 1968.

3. *The Health Consequences of Smoking*, suppl, publication 1696, Public Health Service, 1967.

4. Auerbach, O.; Hammond, E.C.; and Garfinkel, L.: Smoking in Relation to Atherosclerosis of the Coronary Arteries, *New Eng J Med* 273:775-779 (Oct) 1965.

5. Strong, J.P., et al: Relationship Between Cigarette Smoking Habits and Coronary Atherosclerosis Heart Disease, abstracted, *Circulation*, 34(suppl 3):31, 1966.

6. Viel, B.; Donoso, S.; and Salcedo, D.: Coronary Atherosclerosis in Persons Dying Violently, *Arch Intern Med* 122:97-103 (Aug) 1968.

7. Doyle, J.T., et al: The Relationship of Cigarette Smoking to Coronary Heart Disease: The Second Report of the Combined Experience of the Albany, NY, and Framingham, Mass, Studies, *JAMA* 190:886-890 (Dec 7) 1964.

8. Kahn, H.A.: "The Dom Study of Smoking and Mortality Among US Veterans: Report on 8½ Years of Observation, *Nat Cancer Inst Monog* 19:1-125 (Jan) 1966.

9. Best, E.W.R., et al: Summary of a Canadian Study of Smoking and Health, *Canad Med Assoc J* 96:1104-1108 (April) 1967.

10. *The Health Consequences of Smoking*, supplement, Public Health Service publication 1696, Public Health Service, 1968.

11. Bing, R.J.; Cohen, A.; and Bluemchen, G.: "Tobacco Alkaloids and Circulation," in *Tobacco Alkaloids and Related Compounds, Proceedings of the fourth International Symposium, Wenner-Gren Center, Stockholm, February 1961*, New York: Pergamon Press, Inc., 1965, p 211.

12. Conley, C.L., et al: Hematocrit Values in Coronary Artery Disease, *Arch Intern Med* 113:170-176 (Feb) 1964.

13. Mc Donough, J.R., et al: The Relationship of Hematocrit to Cardiovascular States of Health in the Negro and White Populations of Evans County, Georgia, *J Chron Dis* 18:243-257, 1965.

14. Burch, G.E., and DePasquale, N.P.: The Hematocrit in Patients With Myocardial Infarction, *JAMA* 180:63-65 (April 7) 1962.

15. Nadeau, R.A., and James, T.N.: Effects of Nicotine on Heart Rate Studies by Direct Perfusion of Sinus Node, *Amer J Physiol* 212:911-916 (April) 1967.

16. Greenspan, K.; Knoebel, S.B.; and Fisch, C.: Effect of Nicotine Upon Human and Canine Cardiac Action Potential and Contractile State, abstracted, *Project for Research on Tobacco and Health 1964-1968: Report to the Profession and Abstracts of Grants*, Chicago, AMA-ERF, June 1968, p 24.

17. Webb, W.R.; Wax, S.D.; and Sugg, W.L.: Cigarette Smoke and Fibrillation Threshold in Dogs, abstracted, *Clin Res* 16:74 (Jan) 1968.

18. Murphy, E.A., and Mustard, J.F.: Tobacco and Thrombosis, *Amer J Public Health* 56:1061-1073 (July) 1966.

19. Murphy, E.A., and Mustard, J.F.: Smoking and Thrombosis, *Nat Cancer Inst Monogr* 28:47-55 (June) 1968.

20. Murphy, E.A.: "Thrombozyten, Thrombose und Gerinnung," in H. Shievelbein (ed.): *Nikotin, Pharmakologie und Toxikologie des Tabakrauches*, Stuttgart, Germany: Georg Thieme Verlag, 1968, pp 139-154.

21. Spain, D.M., et al: Sudden Death Due to Coronary Atherosclerotic Heart Disease: Age, Smoking Habits, and Recent Thrombi, *JAMA* 207:1347-1349 (Feb 17) 1969.

22. Engelberg, H., and Futterman, M.: Cigarette Smoking and Thrombotic Coagulation of Human Blood, *Arch Environ Health* 11:266-270 (Feb) 1967.

23. Astrup, P., et al: The Effect of Tobacco Smoking on the Dissociation Curve of Oxyhemoglobin, *Scand J Clin Lab Invest* 18:450-457, 1966.

24. Ayres, S.M., et al: Systemic and Myocardial hemodynamic Responses to Relatively Small Concentrations of Carboxhemoglobin (COHB), *Arch Environ Health* 18:699-709 (April) 1969.

25. Seltzer, C.C.: Constitution and Heredity in Relation to Tobacco Smoking, *Ann NY Acad Sci* 142:322-339 (March) 1967.

26. Thomas, C.B.: On Cigarette Smoking, Coronary Heart Disease, and the Genetic Hypothesis, *Johns Hopkins Med J* 122:69-76, 1968.

ers were compared, with the consequent displacement of oxyhemoglobin. In addition, carbon monoxide effects a shift to the left of the oxygen-hemoglobin dissociation curve, which may result in a decreased release of oxygen at the tissue level.[23]

On the whole, experimental and clinical investigations bearing on this question are few. The most salient work in this area has been performed by Ayres and associates.[24] In 26 human subjects before and after carbon monoxide inhalation, these investigators found no significant change in oxygen tension. In another experiment, after exposure to carbon monoxide, coronary blood flow increased significantly in seven non-CHD patients but not in four patients with arteriographically proven CHD. In the patients with CHD, myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting anaerobic metabolism.

If carbon monoxide does in fact appreciably decrease oxygen extraction at the myocardial level, the matter of oxygen consumption may hinge on the extent of increase in coronary blood flow in normal persons, while in persons with diseased coronary arteries, the increase in blood flow is slight or absent. Hence, it may be a question of the ultimate balance of these opposing forces. In normal persons, there is the presumption that the increased coronary blood flow more than matches the presumed decrease in oxygen extraction. Whether or not this fails to occur in patients with obvious CHD, to such an extent as to "trigger" a coronary event is as yet unknown and much work remains to be done in this area.

Summary

Where do we now stand? Certain facts are clear. It is clear that there is a higher mortality rate from cardiovascular disease in cigarette smokers than in nonsmokers. The epidemiological evidence about duration of smoking, inhalation, amount of smoking, and stopping smoking has been shown to be inconclusive or less supportive with respect to CHD than for smoking and other diseases. A chronic effect of cigarette smoking is not clear and is inconsistent with other information. As far as acute effects are concerned, a series of physiological mechanisms have been advanced whereby cigarette smoking could trigger myocardial oxygen deficits of a critical degree in the presence of impaired coronary circulation due to CHD. This hypothesis has not been reasonably substantiated. Some of the evidence is provocative, but in many instances the hypothesized mechanisms are inadequately documented or not documented at all.

The statistical association of higher mortality from CHD in cigarette smokers still remains to be explained. An explanation may lie in a constitutional and genetic predisposition both to cigarette smoking and CHD. A genetic factor in the etiology of CHD is well accepted, and there is a growing body of evidence that smokers are different from nonsmokers in a large variety of biological ways and behavioral patterns, including "style of life."[25,26] If smokers show a greater tendency toward heart disease than nonsmokers because they are different kinds of people than nonsmokers—more vulnerable constitutional types—this could explain the comparatively low degree of association (mortality ratio of 1.7) of excess heart disease among cigarette smokers. At present, this has not been fully established. More research in this area is vitally necessary.

The *Surgeon General's Advisory Committee's Report* on "Smoking and Health" concluded in 1964 that "male cigarette smokers have a higher death rate from coronary heart disease than nonsmoking males, but it is not clear that the association has causal significance."[1] I believe this is where we still stand.

We are mindful that absolute proof is unattainable. We are also mindful, however, of the hazards of inadequate knowledge. More work must be done and new information gathered until the crucial questions are illuminated.

Assuredly, this opinion cannot be satisfying to those readers who are seeking a yes and no answer to the question whether or not cigarette smoking carries a serious risk of CHD. Fair-minded persons will concede that this opinion is mainly due to the unsatisfactory state of the evidence, which only time and more intensive study will resolve.

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